amount of a centrally-acting acetyl cholinesterase inhibitor having a half life of from one to eleven hours wherein the acetyl cholinesterase inhibitor is formulated so as to delay its activity for a predetermined period of from four to twelve hours.

Please delete claims 2 and 6.

Please amend claim 21 to read as follows

21 (Amended) A method of treatment of a patient suffering from a disease or condition in which it is desirable to administer a centrally-acting acetylcholinesterase inhibitor which comprises administering a dosage form of a pharmaceutical composition which comprises an effective amount of a centrally-acting acetyl cholinesterase inhibitor having a half life of from one to eleven hours wherein the acetyl cholinesterase inhibitor is formulated so as to delay its activity for a predetermined period of from four to twelve hours.

Please delete claims 23 and 27.

REMARKS

Independent claims 1 and 21 have been amended to define the nature of the acetylcholinesterase and the requirements for the formulation more precisely by incorporation of the language of claims 2 and 6 into claim 1 and claims 23 and 27 into claim 21.

As explained in the application and in response to the first action on this application, the present invention provides for the first time dosage formulations and methods of treatment that take account of certain side effects that can arise when using centrally acting acetylcholinesterase inhibitors. While providing significant benefits to their users, such compounds also have the effect of keeping persons taking them awake, thereby creating problems for the care givers. By delaying the release of the active compound for a predetermined period of time and using acetyl cholinesterase inhibitors having a half life that is not too long, such problems can be overcome. The prior art does not point to this.

The examiner argues that, although Shapiro and Brossi do not provide a motivation to

combine their teachings to produce what is claimed, Conte provides the missing link. This is not so. Conte is concerned solely with drugs that require delivery at the right time to be active. The present invention relates to making sure that drugs are not delivered at the wrong time so as to cause unwanted side effects. Nothing in Conte points to the use of his invention to solve the problem solved by the applicant. Nothing in any of the cited art points to their being any motivation to control the rate of release of acetyl cholinesterase inhibitors for a predtermined period of time in the range four to twelve hours. With hindsight, the issue of delay to promote activity and delay to prevent another activity may seem similar. But only after reading the present application. There is no reason to combine the references cited. Case law has made it clear that when combining references "while the references need not expressly teach that the disclosure contained therein should be combined with another, the showing of combinability must be clear and particular". Ruiz v. A. B. Chance Co. 57 USPQ2d 1161 (Fed. Cir. 2000). The examiner has made no such showing. Even if one did combine the references one would still not reach the present invention since one would not have read the combination as being relevant to the formulation of acetyl cholinesterase inhibitors for whose basic action the time of delivery is not of any particular significance.

Shapiro is a wide-ranging patent in which he proposes about 50 drugs, acetylcholinesterase inhibitiors among them, for the treatment of about 50 diseases, Alzheimer's among them, with the addition of carbonyl trapping agents, or the carbonyl trapping agents alone. Brossi wants to make physostigmine analogs, and states specifically (column 9, lines 27 and 28) "Delayed and extended release formulations can also be used." The date is 1990. Conte designed devices "to fulfill the specific therapeutic needs of such diseases, which depend on circadian rhythmicity ... for the time-programmed administration of the active ingredients. Such dosage forms should release the drug both at the best possible rate and at the best possible time." However, there is no reason to connect the teachings of these documents. There is no motivation to apply the delayed action of Conte to treatment of Alzheimer's, which does not have diurnal variation, as well as the concept that improper treatment can cause both short and long term adverse consequences.

The reason to delay treatment with a cholinesterase inhibitor is explained in the present application and is based on the endogenous circadian variation in the activity and the sensitivity

of the cholinergic system, which regulates receptors, release and degradation to prevent cholinergic activity at night.

The present invention does not involve treatment at a certain time, because this disease could well be treated all the time, but aims to avoid the immediate (nocturnal activation) and long-term (counterregulatory) consequences of ill-timed activation of a system redundantly programmed to have down-time. Giving a drug which you want to disappear by evening means you have to give the whole dose every day. You have to go from 0 to 100%. The rate of rise of a cholinesterase inhibitor correlates with the degree of nausea and/or dizziness it produces. Thus, a fast rate of rise is, at least early in treatment, undesirable. A second reason is that one would like a patient to wake up in the treated state. Any patient, but particularly one living at home, would best take the morning dose while still under the therapeutic effect of the day before. The delayed release the applicant has proposed is may be taken while the prior day's dose is still active, to permit inactivity during sleep, and to slowly resume the drug effect as morning approaches, as would happen to acetylcholine naturally.

It is therefore submitted that the invention as claimed is clearly not obvious over the combination of Shapiro, Brossi and Conte cited by the examiner because there is no motivation in the art to combine them because the reasons given in Conte for use of a rate-controlled delivery device had no relevance to the use of acetylcholinesterase inhoibitors which were used to treat diseases such as A;zheimer's disease where treatment is not controlled by the circadan rhythm. *A fortiori* there was no motivation to apply the teachings of Conte to the use of drugs having the half life now specified and to control the period of delay to that now specified. The specification of these parameters now confines the claims to compositions and methods where the activity of the drug peaks within a relatively short period after release and where the formulation is designed to delay that release until a time where the side effects of the drug, namely increased activity, can best be dealt with by a care-giver.

Turning now to the 35 USC 112 rejection, one skilled in the art well knows the half life of the drugs being administered. This is part of the standard pharmacology published on all drugs. Therefore selection of the drug and formulating it for an appropriate period of delayed release is well within the competence of those skilled in the art. Many of the drugs in question will by

galanthamine or lycoramine or their derivatives. However, the applicant should not be forced to restrict her claims to drugs of these particular types when the scope of the invention is broader and those skilled in the art will know how to implement it.

Turning now to the new citations of Opitz and Moorman, it is submitted that neither of these either anticipates or renders obvious the invention as claimed.

Moorman teaches the use of galanthamine to treat nicotine addiction. A wide variety of possible formulations is suggested in order to result in administration "over a long period to achieve a lasting effect" (column 4 lines 38-39). However, the objective seems to be to provide for a prolonged release of the drug rather than to delay the start of the release for a predetermined period as required by the present claims. The objective ia apparently a release in a gradual, constant and controlled manner(see column 3 line 49). Such a release does not contemplate an intial delay before any release occurs. Nor does it suggest to one skilled in the art that there should be any delay before such release commences as is required by the present claims.

Opitz teaches the use of galanthamine for treatment of alcoholism. Again the concern is to release the drug in a "continuous and controlled manner" (Column 3 lines 42 - 43). Nothing in this disclosure points towards the applicant's required feature of delaying the initial release of the drug for a defined predetermined period. The claimed invention is therefore clearly novel and not obvious over this disclosure.

In view of the foregoing it is believed that this application is now in order for allowance. An early action to this end is respectfully solicited. If the Examiner believes it would be useful to discuss this matter either personally or in a telephone interview, he is requested to let us know so that this can be arranged.

Respectfully submitted,

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Appendix

1(Amended) A dosage form of a pharmaceutical composition which comprises an effective amount of a centrally-acting acetyl cholinesterase inhibitor **having a half life of from one to eleven hours** wherein the acetyl cholinesterase inhibitor is formulated so as to delay its activity for a predetermined period **of from four to twelve hours.**

21 (Amended) A method of treatment of a patient suffering from a disease or condition in which it is desirable to administer a centrally-acting acetylcholinesterase inhibitor which comprises administering a dosage form of a pharmaceutical composition which comprises an effective amount of a centrally-acting acetyl cholinesterase inhibitor **having a half life of from one to eleven hours** wherein the acetyl cholinesterase inhibitor is formulated so as to delay its activity for a predetermined period **of from four to twelve hours.**